Cytomegalovirus Disease in Renal Transplant Recipients: An Iranian Experience

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Abstract

Background: **Cytomegalovirus is considered the most important infectious cause of mortality and morbidity in organ transplant recipients. In the current study, we evaluate the potential impact of cytomegalovirus infection and cytomegalovirus disease on the outcomes of renal allograft recipients under different conditions.**

Materials and Methods: **We retrospectively analyzed the data from 48 renal transplant recipients who had undergone a transplant at the Baqiyatallah Hospital in Tehran, Iran, between 1984 and 2007. We included all patients with valid laboratory test results for cytomegalovirus infection. Values for *P* less than .05 were considered statistically significant.**

Results: **Overall, 48 patients (2.1%) were documented as developing cytomegalovirus disease. From these, 1 patient (2%) died, and 3 (6%) lost their allograft function. Compared with mycophenolic-acid–based triple immunosuppressive therapy, azathioprine was less likely to induce cytomegalovirus disease and also promised better survival (*P* < .0001 and *P* < .001). Being negative for the anti-cytomegalovirus IgG antibody and receiving an allograft from a positive donor also were associated with cytomegalovirus disease development and poorer patient survival (*P* = .03 and *P* < .0001).**

Conclusions: **Cytomegalovirus infection induces unfavorable outcomes in renal allograft recipients, especially when the infection occurs early on in the posttransplant phase. We suggest close monitoring of cytomegalovirus-positive patients and the use of less-intensive immunosuppressive treatments. Future prospective studies seem necessary.**

Key words: *Cytomegalovirus, Renal transplantation, Donor, Infection, Survival*

Introduction

Cytomegalovirus (CMV) is considered the most important infectious cause of mortality and morbidity in organ transplant recipients. The 3 major complications caused by this virus are CMV disease, super-infection with opportunistic pathogens, and allograft injury (1, 2). Existence of CMV (latent or active) in the donor and recipient (1), the ability of the recipient to mount an immune response to the virus (3), and the type of immunosuppression used (4) are the major intervening factors in the development of CMV and its outcome in kidney transplant recipients. Two distinct populations in kidney transplant recipients are at the highest risk for developing CMV disease and therefore, management of CMV infection in these patients is highly significant for nephrologists in the following 2 scenarios: transplant recipients who become infected primarily at the time of transplant (transmission through donor's organ) and CMV antibody-positive allograft recipients who require induction therapy (4).

In a single-center report in a previous issue of *Experimental and Clinical Transplantation*, Basri and associates provided valuable information on the incidence and outcomes of CMV disease among kidney allograft recipients in Saudi Arabia (5). In the current study, we evaluate the potential impact of CMV infection and CMV disease on the outcomes of renal allograft recipients under different conditions.

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Materials and Methods

We did this retrospective study to analyze the data of patients who had undergone a renal transplant at Baqiyatallah Hospital in Tehran, Iran, between 1984 and 2007. Data were obtained from our local data registry. We included all patients with least 1 valid laboratory result for each of CMV-IgG, CMV-IgM, and CMV-Ag. Cytomegalovirus disease was initially suspected in patients who presented with symptoms of fever, malaise, and laboratory findings suggestive of it during the first few months after transplant and was confirmed by polymerase chain reaction.

Administered immunosuppression protocols were different based on 2 distinct periods: The first period of immunosuppression was from 1984 until 2001 and consisted of azathioprine (1.5 mg/kg/d), cyclosporin (6 mg/kg/d reduced to a maintenance dosage of 3-4 mg/kg/d over a period of 3 months), and prednisolone (50 mg/d reduced to maintenance dosage of 20 mg/d). From 2001 onward, patients received triple immunosuppressive therapy consisting of mycophenolic acid (2 g/d) and cyclosporine and prednisolone at the same dosages as above. Induction therapy using antithymocyte globulin or anti-lymphocyte globulin was preserved in high-risk patients in the early phase of transplant or to treat acute rejection; OKT-3 was not used in any of the studied populations.

SPSS software (Statistical Product and Services Solutions, version 13.0, SPSS Inc, Chicago, IL, USA) was used to analyze the data. Statistical differences between patients' subgroups were assessed using the chi-square test, the Fisher exact test for proportions, and the *t* test for continuous data. A 1-way analysis of variance and Tukey's multiple comparisons tests also were used where appropriate. The Kaplan-Meier method was used for survival analysis. Values for *P* less than .05 were considered statistically significant.

Results

Overall, 2211 patients underwent a renal transplant procedure at our renal transplant center. The mean age for the entire population was 42.9 ± 13.5 years, and 1499 were male patients (67.8%).

Predictors and prognosis of CMV disease

Overall, 48 patients (2.1%) were documented as rehospitalized owing to a diagnosis of CMV infection. From these, 1 patient (2%) died and 3 (6%) lost their allograft function; dialysis was started in these 3 patients.

Evaluating the impact of different immunosuppressive therapies, we found that compared with mycophenolic-acid–based triple immunosuppressive therapy (mycophenolic acid, prednisolone, and cyclosporine), patients undergoing azathioprine-based immunosuppression were significantly less likely to need rehospitalization for the development of CMV disease (0.6% vs 3.2%; $P < .0001$).

We also examined the data to search for a potential association between differences in recipients and their associated donors in terms of anti-CMV antibody positivity and developing CMV disease. We found that kidney transplant recipients who were negative for the anti-CMV IgG antibody and received an allograft from a positive donor (either IgG- or IgM-positive) were more likely to be rehospitalized for CMV disease (6% vs 2%; $P = .03$) even though we routinely used ganciclovir prophylaxis therapy in these patients. When separate evaluations of the recipients' and the donors' seropositivity and development of the disease were done, no relation was found ($P > .05$).

Impact of immunosuppression on outcome of CMV antibody-positive patients

We included all patients in our population (patients whose CMV Ab antibody status was not concomitantly negative with their donors) and excluded patients and their donors who were negative for the anti-CMV IgM and/or IgG antibodies. Using the Kaplan-Meier method, the impact of different types of immunosuppression on the included patients' outcomes was evaluated. Patients undergoing azathioprine-based therapy had significantly better rates of survival ($P < .0001$; Figure 1).

Impact of induction therapy on outcomes for CMV antibody-positive patients

We assessed the impact of induction therapy on the survival of our CMV Ab-positive subjects (included as mentioned in the previous section). Patients who received any of the following agents were considered as receiving induction: antilymphocyte globulin, antithymocyte globulin, daclizumab, or OKT3. A total of 12% of our CMV Ab-positive patients had a history of receiving induction therapy. We detected no differences in the survival rates of patients with or without induction therapy ($P = .572$).

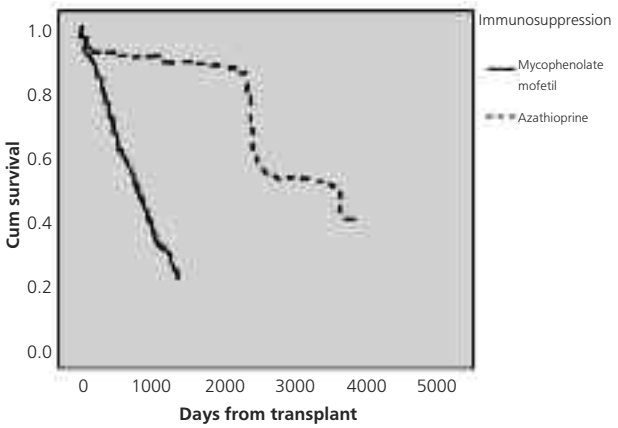

Figure 1. Survival difference between patients with CMV Ab seropositivity regarding their immunosupression protocol.

CMV infection and early posttransplant renal function

We assessed creatinine levels of each of the patients during the first 3 days after transplant and compared them with their anti-CMV antibody conditions: anti-CMV-IgG and anti-CMV-IgM positivity of recipients and their attributed donors. Using an independent samples *t* test, a 1-way analysis of variance, and Tukey's multiple comparisons test, we found no relation between early posttransplant serum creatinine levels and the various CMV antibody conditions ($P = .374$).

CMV infection and late posttransplant patient survival

The potential impact of various anti-CMV antibody conditions (as mentioned in the previous section) on patients' survival also was analyzed. Recipients whose donors were antibody-positive for anti-CMV IgG and IgM and who were negative for the same antibodies were considered as having a risk factor for survival ($P < .0001$; Figure 2). No other conditions were found to be a risk for outcome ($P > .1$ for all).

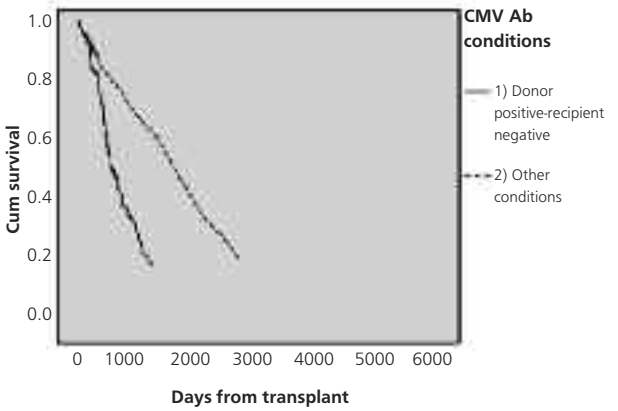

Figure 2. Patients' survival in kidney transplant patients with respect to Their CMV antibody conditions.

CMV infection and late posttransplant renal function survival

We evaluated the impact of various anti-CMV antibody conditions (as previously mentioned) on our patients' renal function survival, one by one. Using the Kaplan-Meier method, we did not find any impact for any of the above-mentioned anti-CMV Ab conditions ($P > .2$ for all).

Discussion

Cytomegalovirus disease has a deleterious effect on morbidity and mortality rates in kidney transplant patients (3). In our study, we also found that using more-potent immunosuppressants also increases the adverse effects of this disease. We demonstrated that compared with azathioprine-based therapy, mycophenolic-acid–based immunosuppression worsened outcomes in CMV Ab-positive patients.

Immunosuppression has been demonstrated to provoke different viral infectious complications in human beings. For example, unusual CMV infections have been reported in patients infected with human immunodeficiency virus (6, 7). Previous studies also have demonstrated that potent immunosuppression protocols are more likely to induce worse outcomes in organ transplant recipients (8-11); although others disagree with this idea (12). We found that patients under a more-potent immunosuppressive protocol (mycophenolate-mofetil–based vs azathioprine-based therapy) are more likely to develop CMV disease. As mentioned above, this agrees with our presumption as well as with most previous reports (8-11). Furthermore, no evidence for a relation between CMV infection and inferior allograft outcome was observed in this study. This finding is in contrast with the report by Basri and associates that stated a possible association between CMV infection and graft failure in renal transplant patients (5).

Interestingly, we also found that kidney transplant patients with CMV infection who received induction therapy were not at a higher risk for unfavorable patient and allograft outcomes. This observation contrasts our presumption about a potential adverse impact for highly potent immunosuppressants on the outcome of viral

infections in organ transplant recipients. Observations from a single institution showed that transplant recipients who were positive for the CMV antibody and who were treated with induction therapy for rejection were particularly susceptible to developing CMV disease (4). However, some previous reports surprisingly corroborate our finding indicating that induction therapy does not increase the risk for complications by opportunistic infections including CMV (13). These discrepancies between different studies may be the result of different types of induction prescribed for their populations as well as different screening and diagnostic criteria (polymerase chain reaction based vs antibody based) for the CMV infection and disease.

For example, one may suppose that the CMV disease attack rate may differ with the monoclonal and polyclonal antilymphocyte antibody preparations that have different action models, although some studies report similar attack rates for CMV disease regardless of the type of induction agent used to treat the rejection (14, 15). Moreover, it has been shown that CMV disease and its consequences can be prevented by prolonged administration (3-4 months) of antiviral therapies (16-18). That said, one may assume that using prophylactic anti-CMV ganciclovir therapy in our at-risk patients might have been responsible for preventing adverse effects of induction therapy. These prophylactic strategies reduce the attack rate of CMV disease; however, it has been reported that this advantage is attenuated in patients who receive induction therapy (19).

We also observed that the risk for CMV disease is highest when recipients are negative for the virus at the time of transplant, while the attributed donors are infected at the same time. This finding is in agreement with those of previous studies that report transplant recipients in whom primary infection develops at the time of transplant (donor: CMV-antibody–positive; recipient: CMV-antibody–negative) have a greater than 50% attack rate of CMV disease (4).

We also found that patients who develop primary infection at the time of transplant have inferior outcomes compared with other patients. This finding suggests that all CMV-negative patients with end-stage renal disease who go on to receive a renal allograft from a CMV-positive donor should receive intensive follow-up care. Although in our patient population, inferior outcomes were observed in these patients despite the administration of prophylactic antiviral treatments, we suggest that these patients are ideally suited to a preemptive approach to prevent CMV disease with prophylactic antiviral agents.

In conclusion, this study showed that CMV infection induces unfavorable outcomes in renal allograft recipients, especially when the infection occurs early on in the posttransplant phase. We suggest that to prevent CMV disease for allograft recipients, these patients should be closely monitored and receive appropriate supportive treatments. Moreover, using less-intensive immunosuppressive treatment for CMV-infected recipients toward the goal of a decreased risk of rejection should be considered. Future prospective studies seem necessary.

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